

## REMARKS

Applicant notes that the prior rejections under 35 USC § 112, second paragraph and 35 USC § 102 are withdrawn.

### Amendment

Claim 17 is amended to emphasize that the comparison step is intended to provide information about the optical contrast enhancing activity of an agent in the sample population or populations that is (are) used in the method. This amendment is made solely for clarification and not for any reason related to patentability.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **“Version with markings to show changes made.”**

### Claim Rejections

Claims 17, 2-7, 9 and 11 stand rejected under 35 USC § 103(a) over Haglund, et al., in view of Hochman, et al. Claims 8 and 10 stand rejected under 35 USC § 103(a) over Haglund, et al., in view of Hochman, et al. as applied to claim 17 and further in view of Newell, et al. These rejections are traversed below.

The Office Action alleges that the Haglund reference compares the behavior of different dyes in staining tumor cells and teaches that dyes can be developed to target specific tumor cells. Applicants believe that this characterization of the reference is somewhat misleading. Haglund does not compare the behavior of different dyes, either for staining tumor cells or for tumor imaging. Haglund uses only one dye, ICG, for tumor imaging. Haglund refers to a literature report of a study involving animal models with blood brain barrier breakdown. From the brief description given in the Haglund reference, it appears that this study mentioned sodium fluorescein and Evans Blue dye in connection with staining normal brain cells (astrocytes), and did not involve tumor tissue. Haglund did not understand the mechanism by which ICG stains human glial tumors (gliomas). He speculates, based on the reported plasma protein binding and clearance characteristics of Evan Blue and on its reported ability to be taken up into normal animal brain cells, that ICG might also be taken up into human brain tumor cells.

The Office Action alleges that Haglund provides motivation for finding dyes with a high signal to noise ratio. While it is true that Haglund states that dyes *can be developed* which target specific tumor cells (page 315 of the reference), this statement is immediately preceded by several paragraphs which reveal a tremendous amount of uncertainty in the use of dyes for tumor imaging (see, e.g., section entitled "Technical limitations, pitfalls, and future studies" that begins on page 314) for reasons that are clearly spelled out in the next several paragraphs on pages 314 and 315. In essence, Haglund *invites experimentation* by suggesting that "once the mechanism of dye perfusion through and into the tumor tissue is better understood, more-specific dyes can be developed to target specific tumor cell lines and these dyes can be modified to provide a larger signal-to-noise ratio". In other words, determining the mechanism is considered a prerequisite for discovering more sensitive dyes.

Applicant maintains that Haglund does not teach or suggest comparing test data with comparison data to identify useful optical contrast enhancing agents. The reference disclosure does not provide the requisite motivation to use optical imaging to identify optical imaging enhancers, as is claimed in applicant's inventive method.

With regard to Hochman, we agree with the Examiner that the Hochman reference gives examples of known dyes- dyes that are safe for in vivo administration and which preferably cross the blood brain barrier. It is also true that Hochman states that *instead of using cutoff filters*, administration of a dye can act as a tissue filter of emr to provide a filter in the area of interest; *for this purpose*, a dye must have particular clearance characteristics in the area of interest (see col. 18, lines 26-30). The Hochman reference teaches the use of ICG for enhanced optical imaging of tumors and teaches a method (enhanced optical imaging) for identifying tumor tissue and distinguishing tumor from normal tissue.

Applicant submits that neither Hochman nor Haglund together with Hochman suggest the method which is claimed in the present application for identifying an optical enhancer agent. This method involves, *inter alia*, exposing a biological material to a *candidate* optical contrast enhancing agent (i.e., an agent that is not known to act as an optical enhancer in the selected biological material), acquiring test data subsequent to exposure of at least one sample population in the biological material, and comparing the test data to comparison data *to reveal changes* that represent the activity of the candidate optical contrast enhancing agent in the test population.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at applicant's claimed invention. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must suggest all the claim limitations of applicant's claims. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. MPEP § 2142, pp 2100-2110. Applicants do not perceive that the Examiner has made a *prima facie* case for the following reasons.

Applicant submits that the Haglund reference, alone or combined with the Hochman reference, would not suggest or motivate a skilled artisan to modify Haglund or combine references to arrive at applicant's claimed method. The naming of dyes that may be suitable for use does not suggest a method for identifying dyes that are useful. While it may perhaps be "obvious to try" to use optical imaging in this way, this is not a proper legal standard for an obviousness rejection.

Furthermore, there is no suggestion in either Hochman or Haglund to combine references. But even if such a suggestion was present, applicant submits that the Hochman reference does not supply the motivation that is lacking in Haglund.

Applicant urges that in making this rejection, the Examiner may have inadvertently constructed a motivation for applicant's method . . . *to find dyes with a high signal to noise ratio or which enhance the sensitivity in imaging tissues*" (see page 3 of Office Action) from portions of each reference taken out of context (e.g., Haglund's *"a larger signal-to-noise ratio"* and Hochman's *"a method for enhancing sensitivity and contrast of the images"*). The motivation for the claimed invention exists only in applicant's specification, and not in the combination of cited prior art references.

Claims 8 and 10 stand rejected as obvious over Haglund in view of Hochman and further in view of Newell. Claim 8 recites the method of claim 17 as applied to multiple sample populations in an in vitro culture system. Claim 10 recites the method of claim 17 as applied to a viable sample population in cell culture. According to the Office Action, Newell teaches imaging of cells in culture using a computerized imaging system, and therefore it would have been

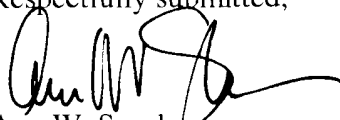
obvious to use Newell's in vitro culture as a sample population with the method of claim 17 with a reasonable expectation of success.

For the reasons discussed above, applicant urges that claim 17 is not obvious over Haglund in view of Hochman, and therefore, claims 8 and 10 are not obvious in view of the secondary reference Newell.

### **Conclusion**

In view of the above remarks, applicant respectfully requests that the Examiner withdraw all claim rejections under 35 USC § 103(a). Favorable reconsideration of the application and early notification of allowance is respectfully requested.

Respectfully submitted,



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In re application of **Daryl W. Hochman**

Application No. **09/326,244**

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the claims:**

Claim 17 has been amended as follows:

17. (Twice Amended) A method for identifying optical contrast enhancing agents useful for enhancing the sensitivity of optical detection of a biological material comprising:

maintaining at least one sample population of the biological material in one of the following systems: a cell culture system; a tissue culture system; an organ culture system; and an intact organism;

exposing the at least one sample population to a candidate optical contrast enhancing agent;

acquiring test data relating to one or more optical properties of the sample population subsequent to exposure to the candidate optical contrast enhancing agent; and

comparing the test data acquired to comparison data relating to the one or more optical properties of the sample population, whereby changes in the one or more optical properties reflected in the test data compared to the comparison data represent [activity of the candidate optical contrast enhancing agent] the optical contrast enhancing activity of said agent in said sample population and identify an agent that is useful for enhancing the sensitivity of optical detection in said population.